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Original Article

Serum vitamin D decreases during chemotherapy: an Australian prospective cohort study

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Background and Objectives: Vitamin D plays an important role in bone and muscle function, and cell proliferation. The impact of chemotherapy and associated behavioural changes such as fatigue and sun avoidance on vitamin D (25(OH) D) is unknown. This study aims to evaluate variations in serum vitamin D during chemotherapy and the predictive value of latitude, season and pre-existing vitamin D deficiency. **Methods and Study Design:** A 12-week prospective cohort study was conducted in chemotherapy-naïve patients in two Australian locations with different sun exposure. Vitamin D deficiency was defined as ≤25 nmol/L and insufficiency 26-50 nmol/L 25(OH) D. Demographics, chemotherapy regimen, nutritional status, sun exposure, geographic location, and season were collected at baseline, 6 and 12 weeks after commencing chemotherapy. **Results:** Eighty-five patients (μ55.3±13.4 years of age; 49% female) were recruited, 96% Caucasian. Fifty-four patients were treated with curative intent (mostly for breast [n=29] or colorectal [n=12] cancers). At baseline, 10 patients were vitamin D deficient and 33 were insufficient. Mean serum 25(OH) D (nmol/L) was higher at latitude -27.5º (Brisbane) than latitude -34.9º (Adelaide) (μ61.9±22.1 vs. μ42.2±19.2, $p<0.001$) and varied according to season (spring: μ46.9±20.3, summer: μ50.8±18.2, autumn: μ76.4±25.2, winter: μ36.5±15.7, $p<0.001$). Serum 25(OH) D decreased with chemotherapy (baseline: μ49.2±22.3, 6-weeks: μ40.9±19.0, 12-weeks: μ45.9±19.7, $p=0.05$), with a significant and more rapid decline in winter and autumn ($p=0.03$). **Conclusions:** Chemotherapy is associated with a decrease in serum vitamin D, particularly during winter and autumn. Investigations into the underlying mechanism and associated potential outcomes with this decrease requires further investigation.

Key Words: vitamin D, 25(OH) D, cancer, chemotherapy, breast cancer

INTRODUCTION

Vitamin D is important for bone health, with vitamin D deficiency leading to osteopenia or osteoporosis in adults. The prevalence of vitamin D (25(OH) D) deficiency varies from 5% in USA, 11% in the South Pacific, 17% in South East Asia and, 27% in Europe.[1] Even in regions of high ultraviolet radiation (UVR) such as Australia, up to 40% of adults have low vitamin D status.[2] The risk factors for deficiency include age, BMI, ambient UVR (e.g. geographic location) and UVR exposure behaviours (e.g. clothing and sunscreen use).[3,4]

In recent years, research focus has shifted from the classical bone and muscle functions of vitamin D to its growth-regulating actions such as the regulation of cell proliferation and differentiation, immune-modulator ac-

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tion, and potential therapeutic roles in disease management. Emerging research suggests the potential role of vitamin D in cancer prevention,[5] prevention of cancer progression[6-9] and reduction in cancer-associated complications such as arthralgia, muscle weakness, and bisphosphonate toxicity.[10-12] In 2017, a meta-analysis revealed that higher levels of circulating 25(OH) D had a 25% lower risk of mortality in breast cancer patients (HR=0.75, 95% CI=0.56 to 0.95; n=9 studies; n=7,262 participants).[13]

Cancer patients have a higher prevalence of vitamin D deficiency than the general population, where up to 67% have insufficiency.[14] In an electronic chart review of over 39,000 adults with solid tumours in the USA, it was concluded that vitamin D deficiency was common, and paradoxically those at greatest risk were the least likely to be tested.[15] This indicates that cancer patients are an 'at risk' group and that there may be additional risk factors for low levels of vitamin D. Two retrospective studies in the USA and France found that those undergoing chemotherapy or with a history of chemotherapy treatment in the past three months were at greater risk of having vitamin D deficiency.[16,17] Although these studies adjusted for diet and UVR exposure at baseline they did not assess the influence of the season during treatment on the changes in vitamin D status.

The actual impact of chemotherapy and associated lifestyle behaviours on serum 25(OH) D concentration is unknown since vitamin D status is not routinely assessed before or throughout chemotherapy. Additionally, it is possible that behavioural changes associated with cancer treatments such as fatigue, decreased time spent outdoors, dietary changes and sun avoidance (incidental and medically advised) may be predictive of low vitamin D status in this group. To address this gap in the current body of evidence, this study aimed to evaluate variations in serum 25(OH) D during treatment in chemotherapy-naïve medical oncology patients in two geographically distinct Australian settings with different levels of sun exposure. The secondary aim was to determine potential predictors of change including age, nutritional status, BMI, gender, location of residence, season and pre-existing vitamin D deficiency and insufficiency on vitamin D levels following chemotherapy treatment.

METHODS

This study was a 12-week observational, prospective cohort study of chemotherapy-naïve (i.e. no prior chemotherapy) patients commencing chemotherapy treatment in two Australian sites located at different latitudes (Adelaide, South Australia: -34.9º; Brisbane, Queensland; -27.5º). A consecutive sample of adult medical oncology patients with a histologically confirmed cancer, which were chemotherapy-naïve and planning to commence chemotherapy within 2 weeks was offered study entry and written informed consent was obtained. This study was approved by the Princess Alexandra Hospital Human Research Ethics Committee (HREC; UCHREC/10/QPAH/22), Southern Adelaide Clinical HREC (126-10), and the University of Queensland (UQ2010000903).

At baseline (commencement of chemotherapy), demographic and clinical data including age, gender, measured height and weight, ethnicity, primary site, treatment intent and planned chemotherapy treatment were recorded. A dietitian trained to assess nutritional risk and status administered the validated Patient-Generated Subjective Global Assessment (PG-SGA) tool.[18] The PG-SGA, sun exposure in the previous 7-days (low <2 hours; moderate 2-12 hours; high >12 hours), and 7-day intake of vitamin D-rich foods (e.g. oily fish and vitamin D fortified milk) were collected at baseline, 6 and 12 weeks after commencing chemotherapy. Data pertaining to chemotherapy regimen, medication and supplement use were collected at baseline and changes were captured during follow-up interviews.

Non-fasting blood samples were taken at baseline, 6 and 12 weeks and collected at the same time as chemotherapy treatment blood draws whenever possible. Serum was separated by centrifugation within 4 hours of collection and stored at -80ºC until analysis. Serum was batch-analysed for 25(OH) D concentrations at the AusSun Research Laboratory at the Queensland University of Technology using Diasorin® liaison semi-automated chemoluminescence immunoassay (DiaSorin). Vitamin D deficiency and insufficiency was defined as <25 nmol/L (<10 ng/mL) and 25-50 nmol/L (10-20ng/mL) 25(OH) D, respectively.[19] The laboratory technician performing the assay was blinded to all personal and medical characteristics of the patients.

Statistical analysis

The STATA statistical software package was used for all analysis (version 12.0, StataCorp, Texas, USA). Baseline characteristics of the subjects were described using mean ± SD for normally distributed continuous variables and median (range) for non-normally distributed continuous variables. Population-averaged effects were obtained using generalised estimating equations with a Gaussian distribution and identity link to estimate the association between patient characteristics and serum 25(OH) D. These models use all available data over the follow up, and take into account correlated repeated measures in the same individual. Patient characteristics that were assessed in univariate analysis were age, gender, BMI, sun exposure, intake of vitamin D rich foods, nutritional status, state of residency (by latitude), treatment period (0, 6 or 12 weeks since start of chemotherapy) and whether or not the patient was currently receiving treatment (yes/no). Variables that were significant at $p<0.1$ in univariate analysis were considered for inclusion in a multivariate model. Age, gender, BMI and chemotherapy status were included in the multivariate model a priori. Interaction terms assessed for inclusion in the multivariate model were those between treatment period and all other covariates. We defined statistical significance as those effects with $p<0.05$ in two-tailed tests.

RESULTS

A total of 85 participants were recruited (n=33 Queensland; n=52 South Australia); however, only 81 were included in the analysis as four participants did not attend the baseline vitamin D blood test (Figure 1). Following

baseline, 14 participants were lost to follow-up. Table 1 describes the demographics and clinical characteristics; participants were similar across the two states (p>0.05; data not shown).

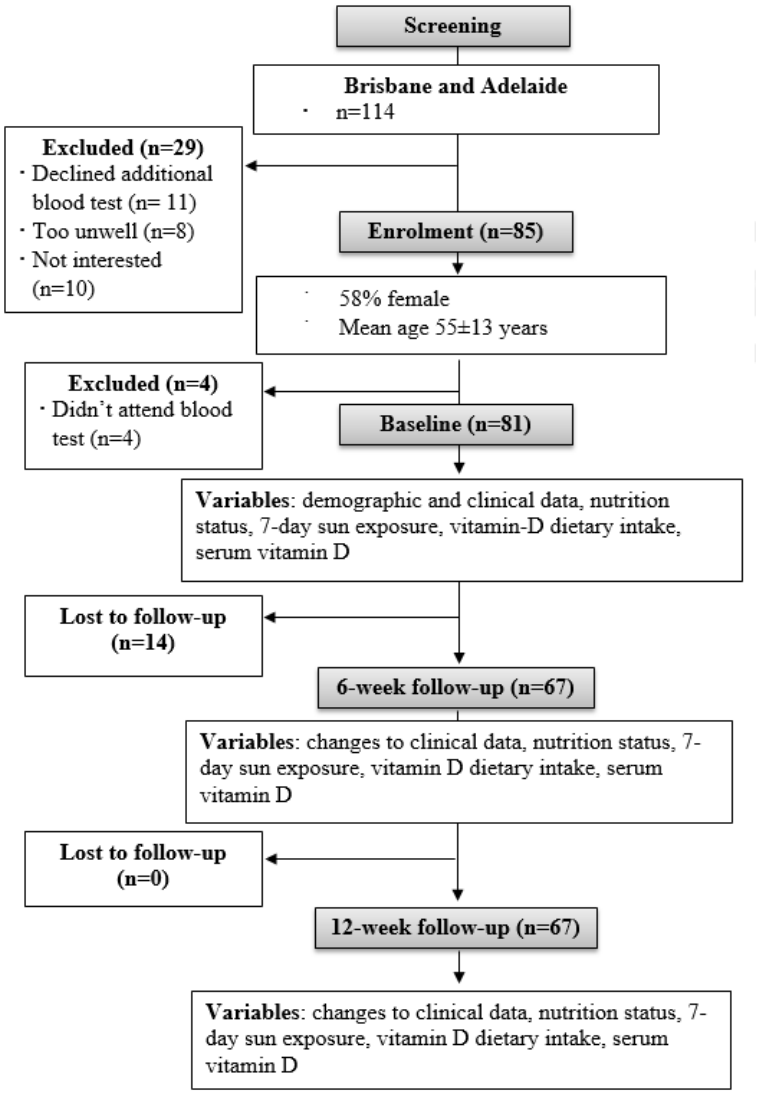

Figure 1. Study design and patient flow

Change in 25(OH) D concentrations

The 25(OH) D serum concentration at baseline was µ49.2±22.3 nmol/L. Ten (12%) patients were vitamin D deficient at baseline and a further 33 (41%) insufficient. Queensland patients had significantly higher serum 25(OH) D concentrations compared with South Australia at baseline (µ61.9±22.1 versus µ42.2±19.2 nmol/L, p<0.001) and 6-weeks (µ49.3±21.4 versus µ37.5±17.1 nmol/L, p=0.02) but not 12-weeks (µ51.9±19.4 versus µ42.8±19.5 nmol/L, p=0.07). Seventy-six (89%) patients were still receiving chemotherapy treatment at 6-weeks follow-up and 55 (65%) patients at 12-weeks follow-up.

Predictors of change

In univariate analysis, treatment period (p=0.004), season (p<0.001), state (latitude) (p<0.001), treatment period x season (p<0.001) and treatment period x state (latitude) (p=0.03) were significant predictors of serum 25(OH) D. These variables as well as nutritional status (PG-SGA) score (p=0.08) and high fish intake (p=0.10) were considered for inclusion in the multivariate model. In multivariate analysis, adjusted for age, gender, BMI and chemotherapy status, serum 25(OH) D concentrations were higher in Queensland compared to South Australia (µ61.9±22.1 versus µ42.2±19.2 nmol/L, p<0.001) and varied significantly according to season (spring: µ46.9±20.3, summer: µ50.8±18.2, autumn: µ76.4±25.2, and winter: µ36.5±15.7 nmol/L, p<0.001). There was a trend towards a treatment period effect with an overall decline in serum 25(OH) D concentrations at 6 and 12 weeks compared to baseline (baseline: µ49.2±22.3, 6-weeks µ40.9±19.0, 12-weeks µ45.9±19.7 nmol/L, p=0.05). Decline also varied according to season (p=0.03 for treatment period x season interaction) with declines in serum 25(OH) D across the 12-weeks in winter (p=0.002 at 12-weeks) and autumn (p=0.004 at 12-weeks), but declines only in the first 6 weeks for summer (p=0.04 at 6-weeks and p=0.41 at 12-weeks) and no declines in spring (p=0.05 at 6-weeks and p=0.86 at 12-weeks). Figure 2 shows the averaged declines for Spring/Summer and Winter/Autumn (p<0.001 for interaction) Compared to baseline values, Vitamin D declined by 11.7±5.4 (p=0.003) more in Autumn/Winter compared to

Spring/Summer and by 25.7±5.0 (p<0.001) in Autumn/Winter compared to Spring/Summer.

When consumption of vitamin D enriched milk and/or high fish intake were considered as a single variable, there was a tendency towards reduced odds of 25(OH) D insufficiency with consumption of either item (OR: 0.463 [95%CI: 0.209-1.030] p=0.059). There were no significant independent associations between 25(OH) D and age, gender, BMI, nutritional status, or vitamin D enriched milk or high fish intake as separate variables. There were no additional independent effect of current chemotherapy treatment (receiving/not-receiving chemotherapy) beyond that ascribed to the treatment period effect (i.e. the time since commencing chemotherapy).

DISCUSSION

This is the first Australian prospective study examining vitamin D changes from the commencement of chemotherapy; and is also the first Australian study to account for factors known to influence 25(OH) D concentrations in this population. This study shows that vitamin D deficiency and insufficiency is common at baseline in Australian cancer
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The decline in 25(OH) D concentrations was season-dependent; which suggests changes in ambient UVR may have influenced serum 25(OH) D concentrations. This hypothesis is further strengthened by the observation that the chemotherapy-associated decline in 25(OH) D concentrations was more pronounced in winter and autumn. The recovery of 25(OH) D observed at 12 weeks was only seen in the summer and spring months. In addition, seasonal clothing and dietary habits, as well as time outdoors, may compound the effects of lower ambient UVR in the cooler months. Intentional and unintentional sun avoidance as a consequence of reduced outdoor physical activity[22] or photosensitisers such as fluorouracil[23] would also reduce skin vitamin D production. Interestingly, patient-reported sun exposure in our study was not associated with 25(OH) D concentrations. This may be explained by the lag time between the reported period of the sun exposure (past week) and the 2-3-week half-life of serum 25(OH) D, suggesting sun exposure needs to be measured over a longer period of time. Researchers should also consider the assessment of clothing and sunscreen habits in the evaluation of sun exposure and vitamin D in chemotherapy patients.

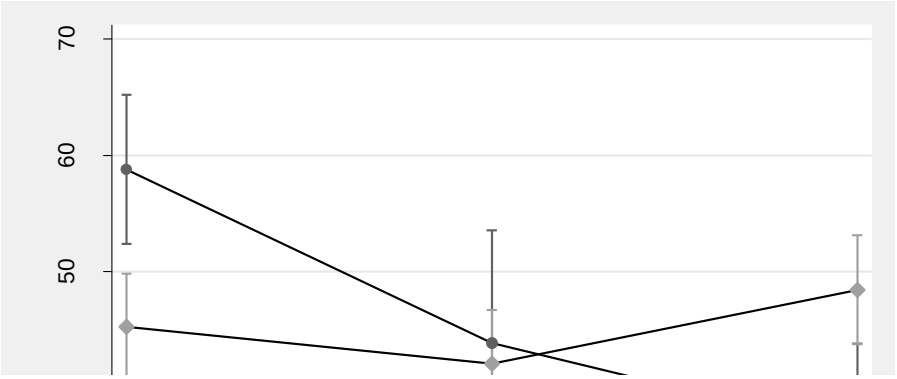

Table 1. Demographic and clinical characteristics of study participants

Characteristic	Result
Age (years), mean±SD	55.3±13.4
Sex, n (%)	
Male	36 (42.3)
Female	49 (57.7)
Ethnicity, n (%)	
Caucasian	81 (95.3)
Other	4 (4.7)
Weight (kg), median (range)	75 (50-151)
BMI (kg/m^2), n (%)	
<18.5 (underweight)	2 (2.35)
18.5-24.9 (normal range)	27 (31.8)
25-29.9 (overweight)	28 (32.9)
≥30 (obese)	28 (32.9)
Nutrition assessment, n (%)	
PG-SGA rating A (well nourished)	67 (78.8)
PG-SGA rating B (moderately malnourished or suspected malnutrition)	18 (21.2)
PG-SGA rating C (severely malnourished)	0 (0.0)
Primary site, n (%)	
Breast	29 (34)
Colorectal	12 (14)
Other	10 (11)
Lymphoma	9 (11)
Leukaemia	7 (8)
Lung	7 (8)
Ovarian	5 (6)
Testis	3 (4)
Unknown primary	3 (4)

BMI: body mass index; PG-SGA: patient-generated subjective global assessment.

The association of chemotherapy and 25(OH) D concentrations may further indicate metabolic mechanisms for vitamin D change. Vitamin D may be converted to inactive metabolites by upregulation of the cytochrome P450 enzymes as a response to chemotherapy. It has also recently been shown that vitamin D-binding protein (DBP) is associated with 25(OH) D concentrations.[24] Powe and colleagues[24] reported a higher prevalence of vitamin D deficiency and a lower concentration of DBP in Black Americans. In patients undergoing chemotherapy, there is a shift in the metabolism of albumin, with much lower levels of this protein in the serum, usually attributed to hepatotoxicity and the acute phase response. Although not measured here, it is plausible that reduced liver function also affects the concentrations of DBP and thus 25(OH) D. It would be interesting to explore the association between chemotherapy and DBP and vitamin D levels in future studies and relate these to cancer outcomes.

While our findings add to the body of evidence that suggests that vitamin D deficiency and insufficiency is common among cancer patients, the evidence to support routine supplementation with vitamin D is insufficient. Although vitamin D (combined with calcium) supplementation in post-menopausal women was found not to prevent all-type cancer incidence,[25] a recent systematic review and meta-analysis found good evidence for a causal link between vitamin D status and genotype with cancer outcome.[13] Interventional research is needed to establish the optimal supplementation dose, treatment period, safety and efficacy of vitamin D supplementation in chemotherapy patients on both short and long-term patient outcomes.

The major limitation of this study was that the follow-up period may have been too short for long-term changes and/or recovery of 25(OH) D concentrations to be observed. The study was also limited in that cancer-related outcomes such as bone turnover markers and muscle function were not addressed. In addition, the diversity of chemotherapy treatments in this sample would not be adequately powered to detect differences between chemotherapy regimens, particularly those that are photosensitising. Future studies should utilise measures of body composition such as DXA or bioelectrical impedance analyses and ultraviolet radiation dosimeter badges in conjunction with sun exposure behaviours to measure UVR exposure.

Conclusion

Chemotherapy is associated with a decrease in serum 25(OH) D for chemotherapy-naïve patients during treatment and this is most pronounced in autumn and winter and at lower latitudes. Further research is needed to determine the underlying mechanism by which chemotherapy may be impacting on 25(OH) D concentrations, the patient-related outcomes associated with this decrease, and interventional approaches for preventing/correcting vitamin D decreases during chemotherapy.

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AUTHOR DISCLOSURES

The authors declare that they have no actual or potential competing interests. The authors have full control of all primary data and agree to allow the journal to review their data upon request. This study was funded by the University of Queensland Early Career Research grant and Queensland Health – Health Practitioner Scheme.

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